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(54) Title: COMBINED THERAPY AGAINST TUMORS COMPRISING NEMORUBICIN WITH RADIATION THERAPY

(57) Abstract: The present invention relates to a morpholinyl anthracycline derivative for use as radiosensitizer, to be administered in combination with radiation therapy so that a synergistic effect can be revealed

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Title

Combined therapy against tumors comprising nemorubicin with radiation therapy

Field of the invention

- 5 The present invention relates to the field of cancer treatment and provides an antitumor therapy comprising the combined use of a therapeutically effective amount of a morpholinyl anthracycline derivative with radiation therapy.

Background of the invention

- 10 Cancers are a leading cause of death in humans and in animals; surgery, radiation and chemotherapy are the useful means to fight cancers.

In particular, chemotherapy combined with radiation therapy is a known modality of treatment of neoplastic diseases.

- 15 The treatment of tumours with ionising radiation, also referred to as radiation therapy, is extensively used in cancer therapy as it provides destruction of tumour cells together with inhibition of tumour cell growth, by a direct effect of radiation on DNA as target molecule or by an indirect effect produced by intermediary radiation products such as the formation of free radicals.

- 20 Some anticancer compounds, which are known as being cytotoxic *per se*, are also endowed with radiosensitisation activity as they are capable of inducing DNA radiation damage in response to ionizing radiation and hence of increasing the sensitivity of cancerous cells to the effect of the ionising radiation.

- 25 So far, the possibility of combining both cytotoxic agents, e.g. a given radiosensitiser, and radiation therapy, with the expectation of getting a supra-additive antitumor effect in comparison to the single cytotoxic alone, is of utmost importance in cancer therapy.

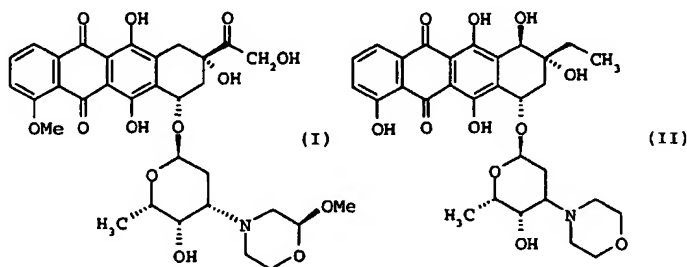
Among the several compounds endowed with antitumor activity and also known as possessing radiosensitisation activity see, for instance, cisplatin, gemcitabine, navelbine, tomudex, nicotinamide, paclitaxel, docetaxel, simvastatin and topotecan.

- 30 The development of new effective cytotoxic agents acting as radiosensitizers intended for combination with radiation therapy can be considered as an unmet medical need in the field of anticancer therapy.

The present invention fulfils such a need by providing an anthracycline derivative, which is a morpholinyl anthracycline derivative for use as radiosensitizer, administered in combination with radiation therapy, so that a synergistic effect can be revealed.

Description of the invention

It is therefore a first object of the present invention a combined preparation comprising a morpholinyl anthracycline derivative having formula (I), formula (II)



a pharmaceutically acceptable salt or a pharmaceutically active metabolite thereof, administered in combination with radiation therapy.

It is a second object of the present invention a morpholinyl anthracycline derivative having formula (I), formula (II), a pharmaceutically acceptable salt or a pharmaceutically active metabolite thereof as defined above, for use as a radiosensitizer agent.

According to the present invention, a preferred morpholinyl anthracycline derivative is the morpholinyl anthracycline derivative of formula (I), more particularly in the form of its hydrochloride salt.

As used herein, the term "metabolite" embraces all derivatives resulted from an enzymatic biotransformation of a morpholinyl anthracycline derivative according to the invention. The chemical reactions of enzymatic biotransformation are classified as phase-I or phase-II reactions.

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As used herein, the term "pharmaceutically acceptable salt" refers to those salts, which retains the biological effectiveness and properties of the parent compound. Such salts include acid addition salt which is obtained by reaction of the free base of the parent compound with inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, phosphoric acid, sulfuric acid and perchloric acid and the like, or with organic acids such as acetic acid, maleic acid, methanesulfonic acid, ethanesulfonic acid, tartaric acid, citric acid, succinic acid and the like, preferably hydrochloric acid.

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15 The morpholinyl anthracycline of formula (I) namely 3'desamino-3'[2(S) methoxy-4-morpholinyl] doxorubicin, also known as nemorubicin, is a doxorubicin (DX) derivative different from classical anthracyclines, obtained with the substitution of the -NH₂ at position 3' in the sugar moiety with a methoxymorpholinoyl group.

As used herein, the term "nemorubicin" includes, unless otherwise specified, the morpholinyl anthracycline derivative of formula (I) and its pharmaceutically acceptable salts, especially the hydrochloride salt.

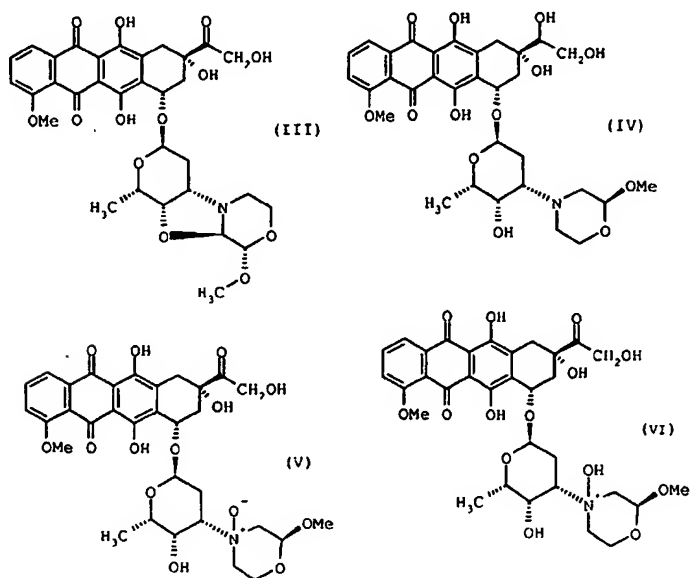
20 Nemorubicin, synthesized in the course of a research program aimed at identifying new anthracyclines with at least partially novel modes of action, effective against anthracycline resistant tumors and possessing broad spectrum of antitumor activity, was disclosed and claimed in Bargiotti et al., US patent No. 4,672,057.

25 Compared to doxorubicin (DX), nemorubicin is significantly more potent *in vivo* than *in vitro*. This observation suggested an *in vivo* metabolism of the drug to potent metabolite/s. In *in vitro* experiments, in the presence of mouse, rat and human liver microsomal enzymes, nemorubicin is metabolized to potent metabolite/s. Microsomal activation appears to occur also *in vivo* since nemorubicin is highly effective on liver metastases.

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Nemorubicin is currently undergoing clinical evaluation; clinical data obtained so far suggest an interesting affinity of nemorubicin for liver lesions, even in tumor types resistant to conventional chemotherapy.

- 5 Examples of identified metabolites of nemorubicin are compounds of the below formulae (III) to (VI)



- 10 The metabolites of the above formulae (III), (IV) and (V) have been described, e.g., in Beulz-Riche et al, *Fundamental & Clinical Pharmacology* 15 (2001), 373-378. Fraier et al. have developed and validated a selective and sensitive liquid chromatography-tandem mass spectrometry (LC-MS-MS) method for quantitative determination of nemorubicin, and its reduced metabolite of the above formula (IV)
- 15 in human plasma (see *Journal of Pharmaceutical and Biomedical Analysis* 2002, 30(3), 377-389).

The metabolites of the above formulae (III), (V) and (VI) are also active antitumor compounds "per se".

The preparation of the compound of formula (III) may be carried out, for example, following the procedure disclosed in GB 2325067.

- 5 The preparation of the compounds of formula (V) and (VI) may be carried out, for example, following the procedure disclosed in GB 2294495.

The compounds of formulae (III) to (VI) may also exist in the form of a pharmaceutically acceptable salt; in this case, preferred salts are hydrochloride salts.

- 10 In a further aspect, the present invention embraces combined preparations comprising a compound of the above formula (III), (IV) (V) or (VI) administered in combination with radiation therapy.

- 15 MX2, a morpholinyl anthracycline belonging to the family of 3'-deamine-3'(4-morpholinyl) derivatives of 10-hydroxy-13-deoxocarminomycin, was described and claimed in Otake et al., US patent no. 4,710,564.

MX2 is active *in vitro* and *in vivo* on tumor cells resistant to anthracyclines and presenting the multi-drug resistant *mdr* phenotype.

- 20 No cross-resistance was observed on tumor cells resistant to CTX, L-PamAM and cDDP.

MX2 is active *in vivo* after i.p., i.v. and oral administration, with good antileukemic and antitumor activity on murine and human tumor models. MX2 is highly lipophilic and less cardiotoxic than DXorubicin. The major dose limiting factor of MX2 is myelosuppression.

- 25 A preferred combined preparation according to the invention comprises a morpholinyl anthracycline of formula (I) as defined above, a pharmaceutically acceptable salt thereof, especially hydrochloride salt, or a pharmaceutically active metabolite thereof, especially a metabolite selected from compounds of formulae (III) to (VI) as defined above, administered in combination with radiation therapy.
- 30

Preferred metabolites according to the present invention are metabolites of the

morpholinyl anthracycline of formula (I) as defined above, particularly the compounds of formulae (III) to (VI) as defined above.

5 In the present description, unless otherwise specified, with the term "radiosensitisation activity" it is intended the aforementioned capability of a compound to act as a radiosensitiser. With the term "radiosensitiser", in its turn, it is intended a compound, which is capable of increasing/improving tumor cells destruction in response to ionizing radiation without an increase in toxicity.

10 As used herein, the term "radiation therapy", also called "radiotherapy", is the treatment of cancer with ionizing radiation. Ionizing radiation deposits energy that injures or destroys cells in the area being treated (the "target tissue") by damaging their genetic material, making it impossible for these cells to continue to grow. Although radiation damages both cancer cells and normal cells, the latter are able to repair themselves and function properly. Radiotherapy may be used, e.g., to treat
15 localized solid tumors, such as cancers of the skin, tongue, larynx, brain, breast, or uterine cervix. It can also be used to treat leukemia and lymphoma (cancers of the blood-forming cells and lymphatic system, respectively).

20 Finally, the term "ionizing radiation" is the term conventionally adopted in the therapeutic field of cancer treatment and includes: electromagnetic radiation (roentgen and gamma radiation) and proton beam radiation therapy. The different ranges of electromagnetic radiations used in clinical practice are superficial radiation or roentgen rays from approximately 10 to 125 KeV; orthovoltage radiation, or electromagnetic radiation between 125 and 400 KeV; and supervoltage, or megavoltage radiation for energies of more than 400 KV. The proton beam radiation therapy protocols refer to
25 treatments ranging from 100 to 250 MeV.

As used herein, "anticancer therapy" refers to all types of therapies for treating cancers or neoplasms or malignant tumors found in mammals comprising humans.

30 The combined preparations according to the present invention would be useful for the treatment of cancer. Preferably, the subject methods and compositions of the present invention may be used for the treatment of neoplasia disorders including

benign, metastatic and malignant neoplasias, and also including acral lentiginous melanoma, actinic keratoses, adenocarcinoma, adenoid cystic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, astrocytic tumors, bartholin gland carcinoma, basal cell carcinoma, bronchial gland carcinomas, capillary, 5 carcinoids, carcinoma, carcinosarcoma, cavernous, cholangiocarcinoma, chondrosarcoma, choroid plexus papilloma/carcinoma, clear cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epitheloid, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, germ cell tumors, 10 glioblastoma, glucagonoma, hemangiblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intraepithelial neoplasia, interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma, leiomyosarcoma, lentigo maligna melanomas, malignant melanoma, malignant mesothelial tumors, medulloblastoma, 15 medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, pituitary tumors, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal cell carcinoma, 20 retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, small cell carcinoma, soft tissue carcinomas, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, undifferentiated carcinoma, uveal melanoma, verrucous carcinoma, vipoma, well differentiated carcinoma, and Wilm's tumor.

25 The term "pharmaceutically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician. This amount can be a therapeutically effective amount.

30 The term "therapeutically effective amount" is intended to qualify the amount of each agent for use in the combination therapy, which will achieve the goal of

improvement in disease severity and the frequency of incidence over treatment of each agent by itself, and/or of amelioration of adverse side effects typically associated with alternative therapies.

- 5 The administration of the constituents of the combined preparations of the present invention can be made simultaneously, separately or sequentially.

It is therefore another object of the present invention the simultaneous, separate or sequential use of the combined preparations of the invention in anticancer therapy.

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As already said, combined preparations according to the invention may be used in anticancer therapy. In a preferred embodiment, combined preparations of the invention may be useful for treating a liver cancer, for example a liver cancer primarily confined to the liver such as, e.g. an hepatocellular carcinoma or a

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The morpholinyl anthracycline derivatives of the combined preparations according to the invention can be administered to a patient in any acceptable manner that is medically acceptable including orally, parenterally, or with locoregional therapeutic approaches such as, e.g., implants. Oral administration includes administering the morpholinyl anthracycline derivatives of the combined preparation in a suitable oral form such as, e.g., tablets, capsules, lozenges, suspensions, solutions, emulsions, powders, syrups and the like. Parenteral administration includes administering the morpholinyl anthracycline derivatives of the combined preparation by subcutaneous,

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intravenous or intramuscular injections. Implants include intra arterial implants, for example an intrahepatic artery implant.

Injections and implants are preferred administration routes because they permit precise control of the timing and dosage levels used for administration.

For example, for treating a patient suffering from a liver cancer as defined above,

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intrahepatic administration of the morpholinyl anthracycline derivatives of the combined preparation may be performed via the hepatic artery. More precisely, the morpholinyl anthracycline derivatives of the combined preparation may be

administered to a patient with either a hepatic metastatic cancer, or with previously untreated primary liver carcinoma, via the hepatic artery directly into the lateral entry of an i.v. line inserted into the bung of an intrahepatic potacath or via a catheter inserted into the hepatic artery.

- 5 In a particular embodiment of the present invention, nemorubicin.HCl may be administered via the hepatic artery as an infusion; the appropriate dose of nemorubicin.HCl, preferably previously dissolved in saline solution, may be mixed with a suitable amount, for example an amount ranging from 1 ml to 100 ml of an agent, for example iodized oil (LIPIODOL™), which remains selectively in a liver
10 tumor after its injection through the hepatic artery.

The actual preferred method and order of administration of the morpholinyl anthracycline derivatives of the combined preparation of the invention may vary according to, inter alia, the particular pharmaceutical formulation of the morpholinyl anthracycline derivatives as defined above being utilized, the particular cancer being
15 treated, the severity of the disease state being treated, and the particular patient being treated.

The dosage ranges for the administration of the morpholinyl anthracycline derivatives according to the invention may vary with the age, condition, sex and extent of the disease in the patient and can be determined by one of skill in the art.

- 20 The dosage regimen must therefore be tailored to the particular of the patient's conditions, response and associate treatments, in a manner, which is conventional for any therapy and may need to be adjusted in response to changes in conditions and/or in light of other clinical conditions.

- 25 A further aspect of the present invention is to provide a method for the treatment of a mammal including a human, suffering from a cancer comprising administering to said mammal a morpholinyl anthracycline of formula (I), formula (II), a pharmaceutically acceptable salt or a pharmaceutically active metabolite thereof as defined above and radiation therapy in amounts effective to produce a synergistic
30 anticancer effect.

It is another object of the present invention a method of treating a tumor in a subject in need thereof, comprising sequentially, separately or simultaneously administering

- (a) a morpholiny derivative of formula (I), formula (II), a pharmaceutically acceptable salt or a pharmaceutically active metabolite thereof as defined above to said subject and
- (b) radiation therapy to said tumor,
- said morpholiny derivative being administered to said subject in an amount effective to potentiate said radiation therapy.

As used herein the term "potentiating" means an increase in the beneficial activity or efficacy of the radiation therapy over that which would be expected from the radiation therapy alone, the morpholiny anthracycline derivative alone, or the sum of the activity of the radiation therapy when administered alone and the morpholiny anthracycline derivative when administered alone.

As used herein, the combined administration of a morpholiny anthracycline derivative and radiation treatment means that the two are administered closely enough in time that the presence of one alters the biological effects of the other. As far as the schedule treatment is concerned, exposure to radiation therapy may either occur simultaneously whilst administering the medicament comprising the morpholiny anthracycline derivative or, alternatively, sequentially in any order.

Simultaneous administration may be carried out by administering the morpholiny anthracycline derivative and radiation treatment at the same point in time but at different anatomic sites or using different routes of administration. Sequential administration may be carried out by administering the morpholiny anthracycline derivative and radiation treatment at a different point in time, for example, the active compounds described herein may be administered orally, parenterally or via intrahepatic administration to a patient prior to receiving radiation therapy.

Preferably, the schedule treatment first comprises administering the morpholiny anthracycline derivative to the patient, which only subsequently is subjected to radiation therapy exposure.

In a further aspect, the present invention relates to the use of a morpholinyl anthracycline derivative of formula (I), formula (II), a pharmaceutically acceptable salt or a pharmaceutically active metabolite thereof as defined above, in the preparation of a medicament in association with radiation therapy for simultaneous or sequential use for the treatment of cancer.

A still further aspect of the present invention is to provide a method for lowering the side effects caused by anticancer therapy with an anticancer agent in mammals, including humans, in need thereof, the method comprising administering to said mammal a combined preparation comprising a morpholinyl anthracycline of formula (I), formula (II), a pharmaceutically acceptable salt or a pharmaceutically active metabolite thereof as defined above and radiation therapy.

In particular, the present invention provides a method for the treatment of patients suffering from a primary or metastatic liver cancer.

By the term "a synergistic anticancer effect" as used herein is meant the inhibition of the tumor growth, preferably the complete regression of the tumor without an increase in toxicity, administering an effective amount of the combination of a morpholinyl anthracycline of formula (I) or (II) as defined above and radiation therapy in amounts effective to produce a synergistic anticancer effect to mammals, including humans.

According to the present invention, the morpholinyl anthracycline derivative may be also administered with additional antitumor agents such as, for instance, topoisomerase I or II inhibitors, e.g. CPT-11, topotecan, 9-amino-camptothecin, 9-nitro-camptothecin, 10,11-methylenedioxy-camptothecin, doxorubicin, daunorubicin, epirubicin, nemorubicin, idarubicin, etoposide, teniposide, mitoxantrone, losoxantrone, amsacrine, actinomycin D; alkylating agents, e.g. melphalan, chlorambucil, mechlorethamine, cyclophosphamide, ifosfamide, busulfan, carmustine, lomustine, semustine, fotemustine, decarbazine, temozolide, thitepa, mitomycin C, cisplatin, carboplatin, oxaliplatin, nedaplatin, lobaplatin; antimicrotubule agents, e.g. paclitaxel, docetaxel, vincristine, vinblastine, vindesine,

vinorelbine, estramustine; antimetabolites, e.g. metotrexate, trimetrexate, tomudex, 5-FU, floxuridine, florafur, capecitabine, cytarabine, azacitidine, gemcitabine; protein kinase inhibitors, e.g. STI571 (Gleevec), ZD-1839 (Iressa), OSI-774 (Tarceva), SU 5416 (Semaxanib), PNU-11248; cyclooxygenase-2 inhibitors, e.g. celecoxib (B-18),
5 valdecoxib (B-19), deracoxib (B-20), rofecoxib (B-21), etoricoxib (MK-663; B-22), JTE-522 (B-23), BMS-347070.

According to a preferred embodiment of the invention, the use of a morpholinyl anthracycline derivative with radiation therapy also comprises the administration of a platinum alkylating agent, e.g. cisplatin, carboplatin, oxaliplatin, nedaplatin or
10 lobaplatin, more preferably cisplatin.

It is a still further aspect of the present invention a combined preparation comprising a morpholinyl anthracycline derivative having formula (I), formula (II), a pharmaceutically acceptable salt or a pharmaceutically active metabolite thereof, administered in combination with radiation therapy, which further comprises administering a
15 therapeutically effective amount of a platinum alkylating agent, especially cisplatin.

In the method of the subject invention, for the administration of the morpholinyl anthracycline derivative according to the invention, the course of therapy generally employed is from about 0.1 mg/m² to about 100 mg/m² of body surface area. More
20 preferably, the course of therapy employed is from about 1 mg/m² to about 1000 mg/m² of body surface area.

As already said, the anticancer therapy of the present invention is suitable for treating, e.g. breast, ovary, prostate, lung, colon, kidney, stomach, pancreas, liver,
25 melanoma, leukaemia and central nervous system tumors in mammals, including humans; in particular it is suitable for treating a liver cancer.

As stated above, the effect of the combined administration of a morpholinyl anthracycline derivative of formula (I), formula (II), a pharmaceutically acceptable salt or a pharmaceutically active metabolite thereof as defined above and radiation
30 therapy is significantly increased (more than additive/synergic effect) in experimental tumor models.

In other words, the combined therapy of the present invention enhances the anticancer effects of the morpholinyl anthracycline (I), formula (II), a pharmaceutically acceptable salt or a pharmaceutically active metabolite thereof or (I) as defined above and of radiation therapy and thus yields the most effective treatment for cancers.

The superadditive actions of the combined preparations of the present invention are shown, for instance, by the following *in vitro* tests, which are illustrative, but not limiting of the combined preparations and methods of the present invention. Other suitable modifications and adaptations of a variety of conditions and parameters normally encountered in clinical therapy, which are obvious to those skilled in the art, are within the scope of this invention.

PHARMACOLOGY

The radiosensitisation effect exerted by a representative compound of the morpholinyl anthracycline derivatives according to the invention, in particular nemorubicin, is shown according to *in vitro* cytotoxicity assays on tumor cell lines. In this respect, two different schedule treatments were evaluated either comprising simultaneous exposure to nemorubicin and to radiation, or sequential exposure to both these therapies in any order, that is drug/radiation or radiation/drug. As control, the effect of cisplatin in combination with radiotherapy has been tested in the same experimental condition.

To define a Sensitization Ratio (SR), the survival of tumor cells being treated with a combination of irradiation and drug exposure ($S_{x \cdot D}$) was compared with the product of survival for drug alone (S_D) and irradiation alone (S_x), as follows: $SR = S_{x \cdot D} / S_D \cdot S_x$.

From the above, if both radiation and drug exerted their cytotoxic effect independently from each other, SR values would be close to 1 whereas, on the contrary, a radiosensitisation effect indicating a synergism between ionizing radiation and drug is characterized by SR values lower than 1 ($SR < 1$).

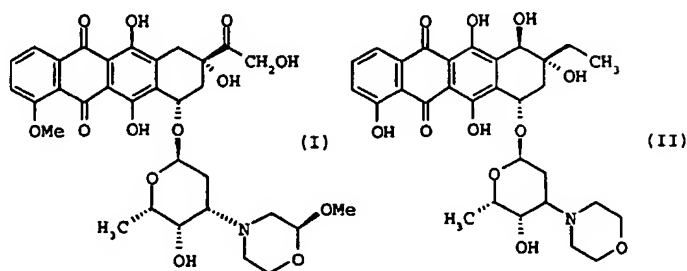
Analysis of the obtained results in any of the experiments being carried clearly indicate that nemorubicin exerts a statistically significant radiosensitising effect.

Supra-additive/synergistic effect has been observed irrespective of treatment sequence. In particular, sensitization is at least comparable to that of cisplatin hence indicating a possible widest range of applications for nemorubicin in combination with radiation therapy.

Claims

1. A combined preparation comprising a morpholinyl anthracycline derivative having formula (I), formula (II)

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a pharmaceutically acceptable salt or a pharmaceutically active metabolite thereof, administered in combination with radiation therapy.

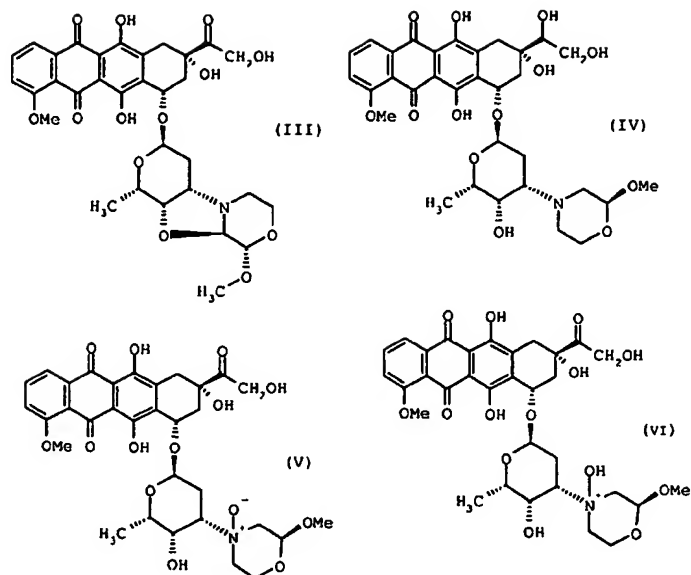
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2. A combined preparation according to claim 1, wherein the morpholinyl anthracycline is of formula (I).

3. A combined preparation according to claim 2, wherein the salt is the hydrochloride salt.

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4. A combined preparation according to claim 1, wherein the metabolite is a metabolite of the morpholinyl anthracycline derivative of formula (I) selected from the compounds of formulae (III) to (VI)



5. A combined preparation comprising a compound of formula (III), (IV), (V) or (VI) as defined in claim 4, administered in combination with radiation therapy.
6. A combined preparation according to claim 1, for use in the treatment of cancer.
7. A combined preparation according to claim 5, for use in the treatment of cancer.
8. Use of a morpholinyl anthracycline derivative having formula (I), formula (II), a pharmaceutically acceptable salt or a pharmaceutically active metabolite thereof as defined in claim 1, as radiosensitizer.
9. Use according to claim 8, wherein the morpholinyl anthracycline derivative is of formula (I).

10. Use according to claim 9, wherein the salt is the hydrochloride salt.

11. Use of a morpholinyl anthracycline derivative of formula (I), formula (II), a
pharmaceutically acceptable salt or a pharmaceutically active metabolite thereof as
5 defined in claim 1, in the preparation of a medicament in combination with radiation
therapy for simultaneous, separate or sequential use for the treatment of cancer.

12. A method of treating a mammal including a human, suffering from a cancer
comprising administering to said mammal a morpholinyl anthracycline of formula (I),
10 formula (II) or a pharmaceutically acceptable salt or pharmaceutically active
metabolite thereof as defined in claim 1 and radiation therapy in amounts effective
to produce a synergistic anticancer effect.

13. A method according to claim 12, wherein exposure to radiation therapy may
15 either occur simultaneously whilst administering the medicament comprising the
morpholinyl anthracycline derivative or, alternatively, sequentially in any order.

14. A method of treating a tumor in a subject in need thereof, comprising
sequentially, separately or simultaneously administering

20 (a) a morpholinyl derivative of formula (I), formula (II) or a pharmaceutically
acceptable salt or metabolite thereof as defined in claim 1 to said subject and

(b) radiation therapy to said tumor,
25 said morpholinyl derivative being administered to said subject in an amount effective
to potentiate said radiation therapy.

15. A method according to claim 12, wherein the cancer is a primary or metastatic
liver cancer.

30 16. A combined preparation as claimed in claim 1, which further comprises
administering a therapeutically effective amount of a platinum alkylating agent.

17. A combined preparation according to claim 16, wherein the platinum alkylating agent is selected from cisplatin, carboplatin, oxaliplatin, nedaplatin and lobaplatin.
- 5 18. A combined preparation according to claim 17, wherein the platinum alkylating agent is cisplatin.